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In Vitro Activity of Apalcillin Compared with Those of Piperacillin and Carbenicillin Against 6,797 Bacterial Isolates from Four Separate Medical Centers

ARTHUR L. BARRY,[1]* RONALD N. JONES,[2] LEONA W. AYERS,[3] THOMAS L. GAVAN,[4] E. H. GERLACH,[5] AND HERBERT M. SOMMERS[6]

The Clinical Microbiology Institute, Tualatin, Oregon 97062,[1]; Kaiser Permanente Regional Laboratory (Oregon Region), Clackamas, Oregon 97015[2]; The Ohio State University Medical Center, Columbus, Ohio 43210[3]; The Cleveland Clinic Foundation, Cleveland, Ohio 44106[4]; Saint Francis Hospital, Wichita, Kansas 67214[5]; and Northwestern Memorial Hospital, Chicago, Illinois 60611[6]

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Quantitative susceptibility tests were performed in four separate medical centers, in which apalcillin was compared with piperacillin and carbenicillin. Data from tests of 6,797 isolates confirmed that apalcillin and piperacillin had nearly identical spectra of activity but that apalcillin was significantly more active against *Pseudomonas aeruginosa* (MIC required to inhibit 90% of strains, 2.0 versus 64 μg/ml) and *Acinetobacter calcoaceticus* subsp. *anitratus* (MIC required to inhibit 90% of strains, 2.0 versus 16 μg/ml). Against 166 anaerobic bacterial isolates, apalcillin demonstrated in vitro activity.

Apalcillin is a naphthyridine derivative of ampicillin. It has a broad spectrum of antibacterial activity, including activity against *Pseudomonas aeruginosa* (1, 4–8). The present report compares apalcillin with piperacillin and carbenicillin against all bacterial isolates that were selected for antimicrobial susceptibility testing in four separate institutions over a 45- to 60-day period. Three laboratories utilized broth microdilution tests, and one utilized agar dilution tests; all followed the procedures outlined by the National Committee for Clinical Laboratory Standards (3). Standard quality control strains (*Staphylococcus aureus* ATCC 29213, *Streptococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, *P. aeruginosa* ATCC 27853) were tested in each laboratory throughout the study period (Table 1). All four institutions provided essentially identical MICs for the control strains. Among those species with enough strains to warrant comparisons between laboratories, MICs required to inhibit 50% of strains (MIC_{50}s) were identical in all four laboratories. Consequently, the data were combined for presentation in this report.

During the study period, tests were performed with 3,452 members of the family *Enterobacteriaceae*, 983 nonenteric gram-negative bacilli, 1,060 streptococci, and 1,032 staphylococci. These isolates are representative of the types of microorganisms normally encountered in the participating laboratories.

Data accumulated with the *Enterobacteriaceae* are summarized in Table 2. Apalcillin was essentially as effective as piperacillin against most species. However, the *Serratia marcescens* isolates were generally more susceptible to piperacillin than to apalcillin (MIC_{50}s, 2.0 and 8.0 μg/ml, respectively). At 64 μg/ml, both drugs inhibited 97.5% of the *Serratia marcescens* isolates. Only 73% of the *Enterobacteriaceae* were susceptible to carbenicillin (MIC, ≤128 μg/ml), whereas 92% were susceptible to apalcillin and piperacillin (MIC, ≤64 μg/ml).

Table 3 summarizes data with nonenteric gram-negative bacilli and streptococci. Apalcillin was significantly more active than piperacillin against *P. aeruginosa* (MIC_{90}s, 8.0 versus 64 μg/ml; MIC_{50}s, 2.0 versus 4.0 μg/ml) and against *Acinetobacter calcoaceticus* subsp. *anitratus* (MIC_{90}s, 8.0 versus 64 μg/ml; MIC_{50}s, 2.0 versus 16 μg/ml). Among the *P. aeruginosa* isolates, 11.5% were resistant to carbenicillin (MIC, >128 μg/ml), 5.3% were resistant to piperacillin (MIC, >64 μg/ml), and only 0.7% were resistant to apalcillin (MIC, >64 μg/ml). Apalcillin also demonstrated superior activity against *Pseudomonas maltophilia* (MIC_{50}, 8.0 μg/ml; MIC_{90}, 64 μg/ml).

Against the streptococci, apalcillin and piperacillin demonstrated comparable activities. Both drugs inhibited the *Streptococcus faecalis* isolates (MIC_{90}, 4.0 μg/ml for both drugs), but carbenicillin was much less effective (MIC_{90}, 128 μg/ml). Additional tests were performed with 862 *Staphylococcus aureus* isolates and 440 coagulase-negative staphylococci (data not shown). β-Lactamase-producing strains were all more resistant to each penicillin, compared with non-β-lactamase-producing strains. Apalcillin, piperacillin, and carbenicillin should not be considered antistaphylococcal drugs since they are inactivated by staphylococcal β-lactamase.

Additional agar dilution MIC data with 166 anaerobic bacteria were obtained by one of the participating laboratories (Table 4). Apalcillin was active against the majority of isolates, including members of the *Bacteroides fragilis* group. At 64 μg/ml, apalcillin inhibited 14 of 14 *B. fragilis* isolates, 1 of 6 *Bacteroides distasonis* isolates, 4 of 5 *Bacteroides ovatus* isolates, 0 of 1 *Bacteroides vulgatus* isolate, and 15 of 17 *Bacteroides melaninogenicus* isolates.

Pharmacokinetic properties of apalcillin differ from those of piperacillin (2). Apalcillin has a longer half-life and is excreted primarily by way of nonrenal routes (mainly hepatic clearance) (2). Whether these pharmacokinetic properties offer a therapeutic advantage remains to be seen. The increased activity of apalcillin against *P. aeruginosa* and *Acinetobacter* spp. should offer a significant advantage over piperacillin.

* Corresponding author.

TABLE 1. Quality control test data for broth microdilution tests with apalcillin and piperacillin

Control strain and antimicrobial agent	No. of tests	Microdilution MICs (μg/ml)		% at mode ± 1 dilution
		Mode (% at mode)	Minimum–maximum	
Pseudomonas aeruginosa ATCC 27853				
Apalcillin	66	≤1.0 (92%)	≤1.0–2.0	100
Piperacillin	66	2.0 (61%)	≤1.0–8.0	99.5
Escherichia coli ATCC 25922				
Apalcillin	69	≤1.0 (74%)	≤1.0–2.0	100
Piperacillin	69	2.0 (100%)	2.0–2.0	100
Streptococcus faecalis ATCC 29212				
Apalcillin	127	2.0 (56%)	0.5–4.0	99.2
Piperacillin	91	2.0 (60%)	1.0–4.0	100
Staphylococcus aureus ATCC 29213				
Apalcillin	64	≤1.0 (62%)	≤1.0–2.0	100
Piperacillin	30	≤1.0 (87%)	≤1.0–2.0	100

TABLE 2. Comparative activities of apalcillin, piperacillin, and carbenicillin against 3,452 *Enterobacteriaceae* strains consecutively isolated at four medical centers

Genus and species (no. tested)	MIC (μg/ml) of following drug for indicated % of strains:								
	Apalcillin			Piperacillin			Carbenicillin		
	50%	90%	% ≤64[a]	50%	90%	% ≤64[a]	50%	90%	% ≤128[a]
Citrobacter diversus (49)	4.0	16	100.0	8.0	16	100.0	128	>128	59.2
C. freundii (118)	2.0	>64	73.7	4.0	>64	76.2	4.0	>128	74.5
Escherichia coli (1411)	1.0	64	90.1	1.0	>64	89.8	4.0	>128	74.7
Enterobacter aerogenes (129)	2.0	64	94.6	2.0	64	96.9	4.0	128	96.0
E. agglomerans (24)	2.0	8.0	100.0	1.0	4.0	100.0	32	>128	73.7
E. cloacae (278)	2.0	>64	89.2	2.0	>64	89.5	4.0	>128	88.4
Hafnia alvei (11)	2.0	64	90.9	2.0	64	90.0	4.0	128	90.0
Klebsiella oxytoca (135)	4.0	8.0	94.8	4.0	16	94.8	>128	>128	6.3
K. pneumoniae (602)	4.0	16	95.9	4.0	16	96.1	>128	>128	43.2
Morganella morganii (79)	2.0	>64	98.8	2.0	64	96.1	2.0	32	95.2
Proteus mirabilis (363)	1.0	1.0	99.7	1.0	1.0	100.0	2.0	2.0	98.5
P. vulgaris (31)	2.0	16	100.0	1.0	16	100.0	32	128	96.4
Providencia spp. (40)	4.0	64	90.0	4.0	>64	89.7	2.0	>128	85.7
Salmonella enteritidis (21)	2.0	>64	81.0	4.0	>64	76.2	4.0	>128	100.0
Serratia marcescens (161)	8.0	16	97.5	2.0	8.0	97.5	8.0	128	92.3
Total (3,452)	2.0	64	92.6	2.0	64	91.7	8.0	>128	72.6

[a] Percentage of strains inhibited by concentrations recognized as breakpoints for defining the susceptible category.

TABLE 3. Comparative in vitro activity of apalcillin, piperacillin and carbenicillin against 983 gram-negative bacilli other than *Enterobacteriaceae* and 1,060 streptococci consecutively isolated at four institutions

Microorganism (no. tested)	Apalcillin			Piperacillin			Carbenicillin		
	50%	90%	% ≤64[a]	50%	90%	% ≤64[a]	50%	90%	% ≤128[a]
Acinetobacter calcoaceticus subsp. *anitratus* (80)	2.0	8.0	96.3	16	64	95.0	16	32	97.5
A. calcoaceticus subsp. *lwoffii* (13)	2.0	4.0	100.0	4.0	8.0	100.0	4.0	128	100.0
Aeromonas hydrophila (12)	2.0	64	100.0	2.0	64	100.0	>128	>128	16.6

TABLE 3—*Continued*

Microorganism (no. tested)	Apalcillin			Piperacillin			Carbenicillin		
	50%	90%	% ≤64[a]	50%	90%	% ≤64[a]	50%	90%	% ≤128[a]
Pseudomonas aeruginosa (817)	2.0	8.0	99.3	4.0	64	94.7	128	>128	88.5
P. fluorescens and *P. putida* (19)	8.0	16	100.0	8.0	64	93.8	>128	>128	100.0
P. maltophilia (42)	8.0	64	90.5	64	64	62.8	128	>128	60.5
Streptococcus faecalis (976)	4.0	4.0	99.6	4.0	4.0	99.5	32	128	100.0
S. faecium (14)	16	16	100.0	2.0	16	100.0	8.0	128	100.0
S. bovis (14)	≤0.25	1.0	100.0	1.0	1.0	100.0	2.0	2.0	100.0
Beta hemolytic (29)[b]	≤0.25	≤0.25	100.0	≤0.25	≤0.25	100.0	≤0.5	≤0.5	100.0
Viridans group (27)	≤0.25	8.0	100.0	1.0	4.0	100.0	8.0	128	100.0

[a] Percentage of strains inhibited by concentrations (μg/ml) recognized as breakpoints for defining the susceptible category.
[b] Includes 27 *S. agalactiae* and 2 *S. pyogenes* isolates.

TABLE 4. In vitro activity of apalcillin against 166 anaerobic bacteria

Microorganism (no. of isolates)	Cummulative % inhibited by concn (μg/ml):				
	≤16	32	64	128	256
Bacteroides fragilis group (32)[a]	68.7	71.9	78.1	90.6	93.7
B. melaninogenicus (17)	70.6	82.3	88.2	100	
Other species (23)[b]	60.9	73.9	86.9	95.6	100
Fusobacterium spp. (22)[c]	100				
Veillonella spp. (11)[d]	54.5	90.9	100		
Other species (61)[e]	100				

[a] Includes 14 *B. fragilis*, 6 *B. thetaiotaomicron*, 6 *B. distasonis*, 5 *B. ovatus*, and 1 *B. vulgatus* isolates. Strains with MIC >64 μg/ml represent 5 of 6 *B. distasonis*, 1 of 5 *B. ovatus*, and 1 of 1 *B. vulgatus* isolates.
[b] Unidentified *Bacteroides* spp. not belonging to the *B. fragilis* group.
[c] Includes 13 *F. nucleatum*, 6 *F. naviforme*, 1 *F. mortiferum*, and 1 *F. varium* isolates and 1 unidentified species.
[d] Includes 7 *V. alcalescens* and 4 *V. parvula* isolates.
[e] Includes 13 anaerobic streptococci and 12 *Peptococcus magnus*, 11 *Peptococcus prevotii*, 10 *Peptococcus asaccharolyticus*, 9 *Clostridium* spp. (4 *C. difficile*), 2 *Eubacterium limosum*, 2 *Lactobacillus* spp., and 2 *Propionibacterium acnes* isolates.

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